

UNIVERSITÉ DE LAUSANNE - FACULTÉ DE MÉDECINE
CLINIQUE INFANTILE UNIVERSITAIRE

Professeur : L.-S. Prod'hom
Professeur : E. Gautier

The early stages of hyaline
membrane disease

THÈSE

présentée à la Faculté de Médecine de l'Université de Lausanne
pour l'obtention du grade de docteur en médecine

par

NAHUM FRENCK

Médecin diplômé de l'Université de Lausanne

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Le Conseil de la faculté de médecine de l'Université de Lausanne, après avoir pris connaissance des rapports favorables de MM. les professeurs

L.-S. PROD'HOM et CLAUDE PERRET

et sans se prononcer sur les opinions du candidat, autorise l'impression de la thèse intitulée :

The early stages of hyaline
membrane disease

présentée par Monsieur

NAHUM FRENCK

Médecin diplômé de l'Université de Lausanne

pour l'obtention du grade de
DOCTEUR EN MÉDECINE

Lausanne, le 15 décembre 1975

Le Doyen :

Prof. G. Candardjis



A Sylviane, Emmanuel et Elodie

A Alex et Sali, mes frères

A mes parents

A Messieurs les Professeurs L.S. Prod'hom et E. Gautier
qui ont éveillé en moi l'amour pour la Pédiatrie et qui
ont su forger le Pédiatre que je suis.

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THE EARLY STAGES OF H M D

1. EVOLUTION OF PaO_2
DURING HYPEROXIA TEST
IN THE FIRST 48 HOURS OF LIFE

by

N. FRENCK, A. Torrado and L. S. PROD'HOM*

Clinique infantile Universitaire
Hôpital Cantonal, Lausanne
Switzerland

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From the FOND NATIONAL SUISSE DE LA
RECHERCHE SCIENTIFIQUE

Respiratory Distress in the newborn is accompanied by hypoxemia associated with a mixed acidosis. This hypoxemia has been shown to be related to a R-L shunt (96, 103, 75, 66), of variable location, either intrapulmonary (94, 100), through the persistence of the fetal pathways (66, 75, 96, 103), or by anomalies in distribution. It has been suggested (75) that by repeated determinations of the overall R-L shunt during the first day of life, it is possible to distinguish several types of respiratory distress in the newborn infant. In type I a large R-L shunt was already found at 4 hours of life followed by a further increase in the first 24 hours. This type was associated with Hyaline Membrane Disease (or idiopathic respiratory distress syndrome) (7, 33, 39, 68, 95, 101). Type III was characterised by a large shunt very early in the postnatal life, decreasing to normal in the first 24 to 48 hours. It was associated with massive meconium aspiration and with perinatal asphyxia (78, 10, 22) where a persistence of fetal shunts and pulmonary hypoperfusion were shown. Type II was characterised by a R-L shunt within the normal range despite marked clinical findings of respiratory distress (75). This type has been related to a delay in the resorption of intraalveolar fluid (8,26). Others authors have suggested that heavy maternal sedation and a mild asphyxia at birth could be the triggering causes (109).

The purpose of this study is to explore the evolution of arterial oxygen tension in infants with Hyaline Membrane Disease (RDS type I), to confirm the identity of this disease, to explain the evolution of the PaO_2 values in regard to gestational age and asphyxia at birth.

Material and methods

The study was carried out on 77 newborn babies with a mean gestational age of 33.3 weeks and a mean birth weight of 1939.1 grams. 26 babies died and they had autopsy proved HHD. A good correlation was found (106) between the clinical and radiological criteria, used in this Center for the diagnosis of HHD and the findings at autopsy.

The diagnosis of HMD was made on clinical (7, 39, 68, 101) and radiological grounds. The chest x-rays were graduated from I to IV based on the severity of the image.

- Type I - ground glass appearance
- Type II - ground glass plus air bronchogram
- Type III - type II plus disappearing of cardiac shadow and diaphragmatic limits
- Type IV - absence of cardiac and diaphragmatic limits, uniform density of the chest.

Infants were cared in Air Shield^R incubators and warm humidified oxygen was administered to maintain the PaO₂ between 50 to 70 mmHg.

35 (45,4%) of the babies needed intubation and assisted ventilation, this was performed with a Bird Mark 7 IPPB respirator. Assisted ventilation was always used as a mechanical aid to respiration and was never considered to be able to change the course of the disease. The indications for assisted ventilation were :

- a) Apnea, not responding to mask ventilation and
- b) Cardio-respiratory decompensation.

These two situations are accompanied by an increase in PaCO_2 over 80 mmHg and a consequent respiratory acidosis and by a fall of PaO_2 to levels lower than 40-50 mmHg while the baby was breathing 100 % oxygen (77).

Umbilical artery and vein catheters were inserted on admission, and all the infants received via the vein catheter a continuous perfusion of Dextrose in water (10 %) (65-75 ml/kg/24 h). Sodium Bicarbonate was given to correct pH when it was lower than 7,25. Hypocalcemia (less than 3,5 mEq/l), and hypoglycemia (less than 30 mg %) were duly corrected. The arterial catheter was used for sampling blood for pH, PaCO_2 , hematocrit, and hemoglobin.

The measurements were done by 4, 8, 12, 20, 24, 28, 36 and 48 hours of life; whenever the measurements were made out of these hours the results were found by extrapolation.

The PaO_2 was measured when the infant was breathing air or a percentage of oxygen necessary to maintain his PaO_2 between 50 and 70 mmHg. Another blood sample was drawn 20 minutes after the baby received 100 % O_2 (Hyperoxia test) (96, 66). This way the PaO_2 increased almost to barometric pressure level irrespective of the level of overall ventilation or of irregularities in ventilation. The effects of impaired diffusion were also eliminated. Therefore, when pure O_2 is breathed for a period adequate to wash out the N_2 in the lungs, any resulting fall in PaO_2 is due to blood that bypassed ventilated alveoli, indicating a R-L shunt (97, 11).

PaO_2 was determined with a polarographic (Clark type) electrode (11 113), that had a 6,25 n Pt cathode, covered with a 25 n polyethylene membrane. A correction factor was used for the PaO_2 readings in view of

observed differences between gas and blood readings obtained with the equilibration technique (30) $(PO_2 \text{ (real)} = (\text{meter reading} \times 1,18) + 1)$. No temperature correction was needed.

R E S U L T S

Evolution of PaO_2

In HMD the PaO_2 values during hyperoxia test are already lower than expected (74, 110) at or before the 4th hour of life (graph. 1). No significant correlation was found between this first value and gestational age, birth weight, acid-base parameters or the degree of severity of the X-ray.

The mean PaO_2 of the entire group falls during the first 20 hours of life, then it is followed by a slow rise (Table 1, graph 1).

PaO_2 and Gestational age

A significant difference in the evolution of PaO_2 was observed between babies with a gestational age equal or lower than 33 weeks and those over 33 weeks gestation. (Fig. 1, Table I). In newborns with a gestational age of 33 weeks or less, at 4 hours of life, the PaO_2 was lower than in the older group and dropped earlier than in the older infants, attaining the lowest value by the 12th hour of life, then the PaO_2 started to rise. The initial 4th hour value was reached by the 28th hour of life. 26 % of these babies died during the first 24 hours of life.

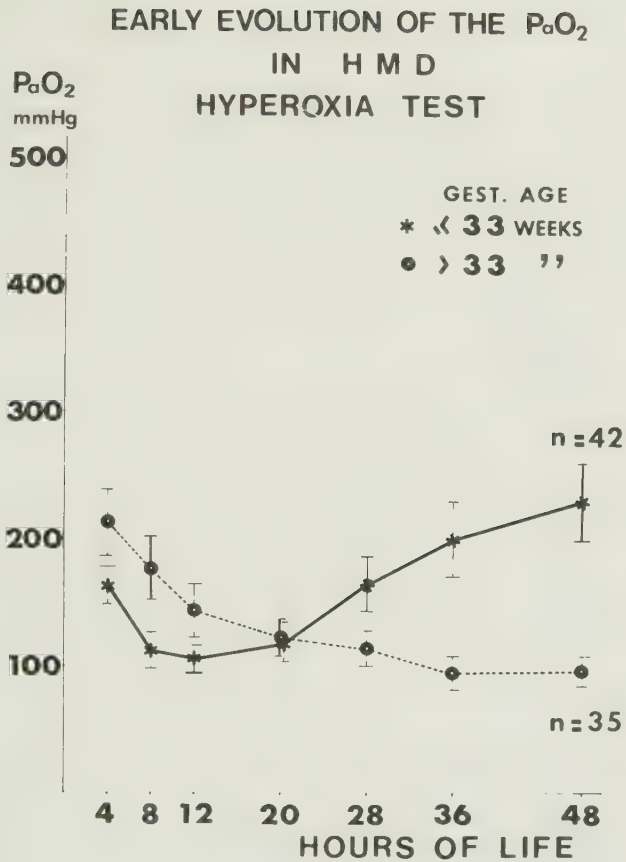
In babies over 33 weeks gestation there is a slow drop reaching the lowest value by 36 hours of life and remaining low until a slow rise starts by the 48th hour of life (See Table I).

PaO₂ and Asphyxia

Neonatal asphyxia is defined by an Apgar score of 4 or less at 1 minute of extrauterine life or a score of 6 or less at 5 minutes. It was also assumed to be present if there was no breathing, or brady cardia of 100 or less at 2 1/2 minutes of life.

Independently of gestational age, babies presenting HMD + asphyxia at birth had a different evolution from babies with HMD without perinatal asphyxia.

At 4 hours of life, the asphyxiated babies had a significantly lower PaO₂ when breathing 100 % O₂ than the non-asphyxiated ones; by 24 hours of life this difference was no more significant (Graph 2).

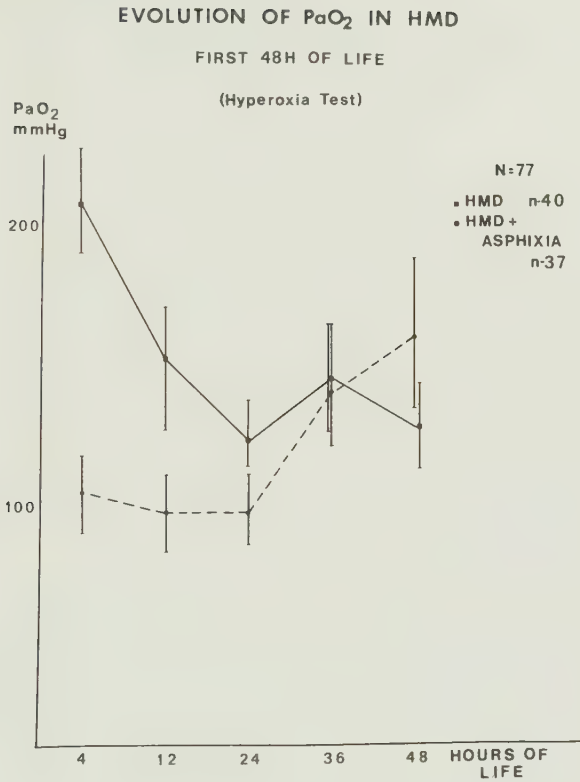


GRAPH 1

T A B L E I

ARTERIAL OXYGEN TENSION (mmHg) BREATHING 100 % OXYGEN IN TWO GROUPS OF INFANTS WITH HMD (MEAN AND SEM)

HOURS OF LIFE	N	WHOLE GROUP	$\leq$ 33 WEEKS GEST.		$>$ 33 WEEKS GEST.		P
			N		N		
4	56	180.9 $\pm$ 15.5	31	160.6 $\pm$ 17.5	25	213.3 $\pm$ 26.4	0.10 $>$ P $>$ 0.05
8	64	139.6 $\pm$ 12.8	39	114.0 $\pm$ 13.5	25	179.6 $\pm$ 23.5	0.02 $>$ P $>$ 0.01
12	62	124.7 $\pm$ 11	36	108.8 $\pm$ 11.8	26	146.0 $\pm$ 19.7	0.10 $>$ P $>$ 0.05
20	51	122.1 $\pm$ 11	28	121.0 $\pm$ 15.5	23	132.3 $\pm$ 14.5	-----
28	53	133.5 $\pm$ 13	24	160.9 $\pm$ 22.3	29	110.8 $\pm$ 12.6	0.05 $>$ P $>$ 0.025
36	43	131.2 $\pm$ 15	16	200 $\pm$ 29	27	95.2 $\pm$ 11.4	P $<$ 0.001
48	40	143.3 $\pm$ 16	13	238 $\pm$ 29.6	27	97.5 $\pm$ 11.5	P $<$ 0.001



GRAPH 2

DISCUSSION

In the 77 infants with HMD the evolution of the PaO_2 during hyperoxia test confirms the one described before (75) for the respiratory distress type I. In the analysis of the individual evolution curves, two different patterns were observed, that for babies at or below 33 weeks gestation and that for babies over 33 weeks gestation.

The initial low PaO_2 value in both groups can be due to pulmonary atelectasis (5, 62, 103), pulmonary hypoperfusion (19, 20), the presence of an extrapulmonary R-L shunt (42, 43, 61, 66, 72, 88, 94) or a combination of them (75, 62). It is well known that in HMD there is a significant decrease in total gas volume and in total lung capacity and this occurs early in the postnatal life (5, 7, 39, 63, 111).

The further fall in PaO_2 (increase in R-L shunt) may be the consequence of the closure of a more important number of alveoli or the reopening of the circulatory fetal pathways. The part played by pulmonary aeration in the PaO_2 evolution pattern is studied in the companion paper.

The different evolution of PaO_2 during the hyperoxia test in babies above and below 33 weeks gestation is difficult to explain. One can speculate that in babies below 33 weeks with HMD there is less surfactant at birth but afterwards production may quickly begin.

In babies over 33 weeks there may be more surfactant initially but the cells producing the substance may be damaged and thus unable to produce this material for a longer period of time.

Some babies presenting HMD that had perinatal asphyxia behave as RDS type III (57). The evolution of their PaO_2 in 100 % oxygen is not different from term babies with perinatal asphyxia but without HMD (78).

In babies with HMD + asphyxia, the initial PaO_2 value is significantly lower than the one found for the whole group of HMD babies and of course, much lower than the normal value.

When calculating R-L shunt, at 4 hours of life, 100 % of babies having a R-L shunt between 60 - 100 % had perinatal asphyxia, against 32 % for a R-L shunt between 20 - 39 % (See graph 3).

The responsible for this low initial PaO_2 could be a low pH which is the product of a mixed acidosis and the asphyxia. This low pH will produce a vasoconstriction of the lung vessels (86), and blood will be diverted, creating extrapulmonary shunts (7), that means a persistence of fetal circulation. These hypoperfusion of the lungs (7) would rather be related to asphyxia at birth than to Hyaline Membrane Disease (78).

PERCENTAGE OF INFANTS IN R-L SHUNT GROUPS

HMD non asphyxiated ☐ HMD asphyxiated ☒



GRAPH 3

THE EARLY STAGES OF H M D

II. EVOLUTION OF R-L SHUNT AND
PULMONARY AERATION IN THE
FIRST 48 HOURS OF LIFE

by

N. FRENCK and L. S. PROD'HOM*

Clinique Infantile Universitaire
Hôpital Cantonal, Lausanne
Switzerland

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RECHERCHE SCIENTIFIQUE

In order to determine the part played by the lungs in the total R-L shunt in HMD, it was found necessary to study the evolution of Functional Residual Capacity as an index of lung aeration in this disease.

The problem raised was : is the evolution of the fall in PaO_2 (increase in R-L shunt) parallel to the evolution of the "pulmonary aeration" or not ? In other words, is the fall in the PaO_2 caused by a "closure" of previously open alveoli or are the alveoli partially open from the very first moment and persist so.

MATERIAL AND METHODS

MATERIALS AND METHODS FOR MEASURING OF THE FRC

The Functional Residual Capacity was measured as an index of pulmonary aeration and was determined by a closed circuit He dilution method (12, 13, 23, 28, 29, 40, 46, 58, 59). For this purpose a small spirometer Parditest (bell containing 180 ml), a katharometer and a rubber mask was preferred to the nasal piece used by some authors (16, 24) or the rigid mask proposed by others (91), because it avoided the problem of air leakage. The system's dead space was determined and the mean of 26 measurements was 1'630,3 ml, with 4,7 % error. Holmgren (40) had a system with a mean dead space of 3'728,0 ml, Engström's (28) had 1'410 ml and Geubelle's (31) had 1'460 ml. The resistance of the system was low because of the presence of two blowers, one in the spirometer and one in the katharometer. The bell movements and therefore the change in volume was recorded in a multichannel Mingograph 81^R.

The system was checked with a dummy lung, with volumes varying between 25 and 100 ml, filled either with air or 100 % O_2 . In both cases a correction factor of FRC (real) = 4,092 + 0,67 FRC (measured), $r = 0,99$

in air and of FRC (real) = 3,302 + 0,67 FRC (measured), $r = 0,97$ in 100 % O_2 was needed. These two formulas are not statistically different. They were used to correct the measured volumes in the babies.

CALCULATION OF THE SHUNT

The shunt was calculated by Berggren's modification of the basic shunt equation :

$$Q_s = \frac{(Hb \times 1,34) (I - SaO_2) + 0,003 (PAO_2 - PaO_2)}{Q_T - (Hb \times 1,34) (I - SaO_2) + 0,003 (PAO_2^* - PaO_2) + (Hb \times 1,34) \times 0,15}$$

$$* PAO_2 = F_I O_2 (BP - PH_2O) - PaCO_2 \left(F_I O_2 + \frac{I - F_I O_2}{RQ} \right)$$

Arterial O_2 saturation was calculated from the PaO_2 and $SaO_2 = \%$ saturation of Hb with O_2 in arterial blood.

The Hb dissociation curve of Nelson et al. (67) was used and a correction of the baby's blood for pH was made (103, 38). The results were consistent with those obtained by Sinclair et al. (92).

The PAO_2 (alveolar O_2 pressure) was calculated from the alveolar air equation (23). The RQ values utilised were 0,89 at 4 and 12 hours and 0,82 at 24 hours (74). The arteric-venous saturation difference was considered to be 0,15 (85) for well and sick babies. The validity of the method for calculating R-L shunt has been discussed formerly by several authors (75, 97, 19).

Blood samples from umbilical artery were drawn and the PO_2 readings were made within 3 min., obviating cooling.

PaO_2 was measured with a Clark type electrode (11, 113) (30). pH and PCO_2 were determined by the Astrup method (2, 3, 84, 89, 90).

Hb was measured by the photometric method (Eppendorf)^R.

FRC was measured in 22 normal newborns as a baseline for comparison. The infants had a mean weight of $2'075 \pm 425$ g (range $1'550 - 2'960$ g).

24 preterm newborns with HMD, with a mean birth weight of $1'798,3$ and a mean gestational age of $32,5$ weeks were studied. All the tests were performed at 4 ± 2 , 12 ± 2 and 24 ± 4 hours of life. The PaO_2 , PCO_2 , pH, hematocrit and acidbase balance were followed. The PaO_2 was determined when the baby was breathing the percentage of O_2 necessary for maintaining his PaO_2 between 50 to 70 mmHg and when breathing 100 % O_2 (hyperoxia test) for 20 minutes.

CONDUCT OF STUDY

The measurements were made as follows :

The rubber mask is applied firmly on the baby's face and he breathes to the open air. When he calms down the stopcock is turned and the baby starts to breath into the closed circuit and continues for 4-5 min. until a plateau is obtained, showing that an equilibrium is reached in the He dilution. (During this time, the He concentration is recorded every 30 sec.).

If the baby cries, the experiment is started again 10 to 15 min. later. The babies supported the test well : in 210 measurements there was one pneumothorax (probably secondary to the test).

With this method the respiratory rate, the tidal volume (V_t), the minute volume (V_E) and the oxygen consumption (VO_2) were also determined (to be published).

RESULTS

The 22 normal newborns presented a mean FRC of 52,4 ml $\pm$ 8,3 (range 34,6 - 65,4). There was a good correlation between FRC and weight ($r = 0,6157$, $0,005$ $p = 0,001$) (Graph 1). The expected FRC of the sick babies was calculated from the formula :

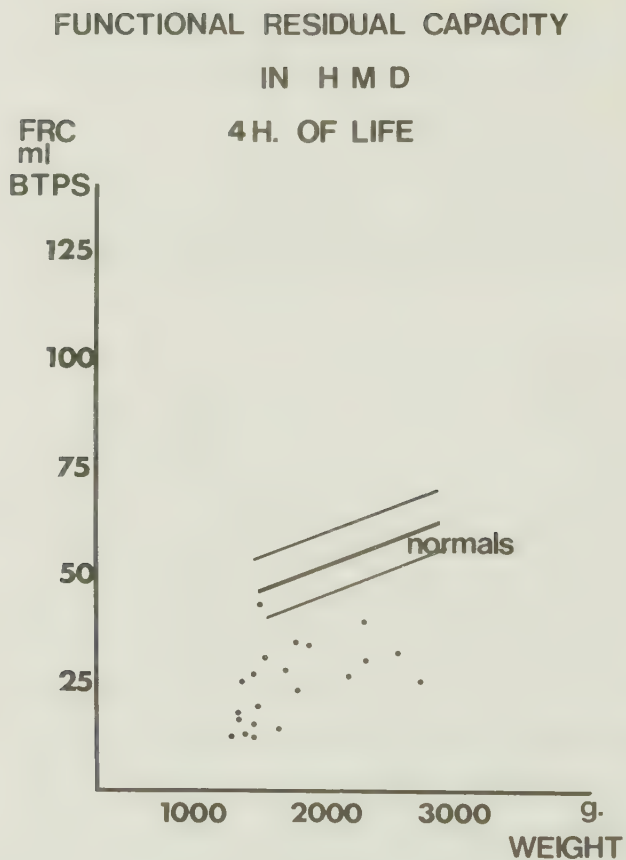
$$\text{Expected FRC} = 27,5 + \text{weight kg } (0,012)$$

The uncorrected values in this study were consistent with the results obtained by other authors (12, 31) using a similar method.

In babies with HHD, at the 4th hour of life, the FRC (in ml BTPS/kg weight) is already lower than normal (Graph 1). At that time there is a good correlation between FRC in % of expected FRC value and right to left shunt (Q_s/Q_T). (Graph 2). No significant correlation was found at 12 or 24 hours of life.

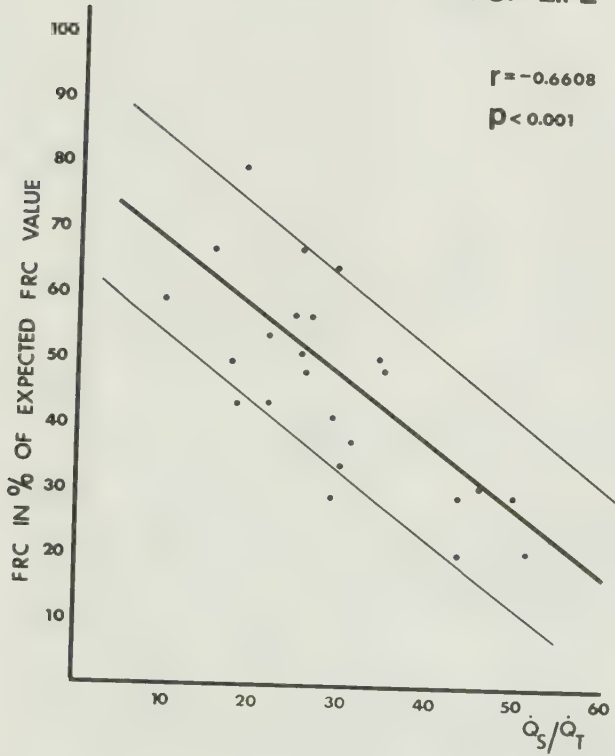
While there is not a significant change of the FRC in % of expected value in the first 24 hours of life; there is an important (42 %) increase in R-L shunt during this period (Table 1, graph 3).

A fall of PaO_2 during hyperoxia test was found in the 24 infants with HHD. When the evolution of PaO_2 and FRC are compared, it is possible to see that PaO_2 drops significantly between 4 and 24 hours of life while the change in FRC is not significant. (Table 1, graph 4).



GRAPH 1

RELATION BETWEEN FRC AND $\dot{Q}_S/\dot{Q}_T$
- 4 H. OF LIFE -



GRAPH 2

TABLE I

MEAN AND SEM

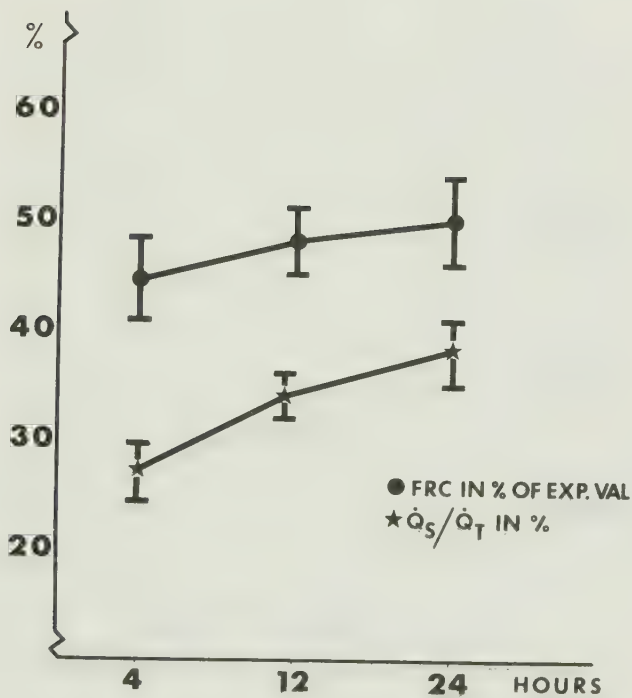
HOURS OF LIFE	PAO ₂ (F _I O ₂ = 1)	R-L SHUNT	FRC % OF EXPECTED VALUE
4 H $\pm$ 2	263.9 $\pm$ 25.5	26.9 $\pm$ 2.3	44.8 $\pm$ 3.8
12 H $\pm$ 2	182.8 $\pm$ 19.2	33.9 $\pm$ 2.05	48.1 $\pm$ 3.9
24 H $\pm$ 4	177.2 $\pm$ 26.5	38.2 $\pm$ 3.04	50.5 $\pm$ 4.2

- 26 -

SIGNIFICANCE OF CHANGE

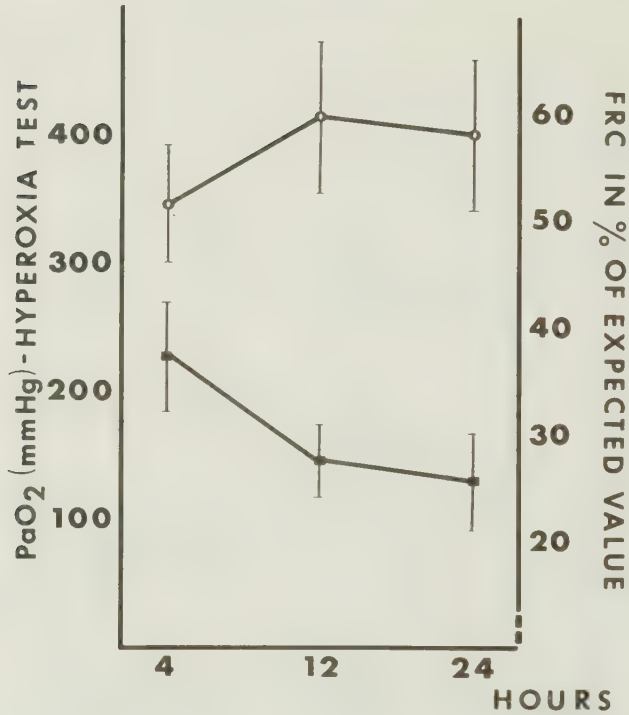
HOURS OF LIFE	PAO ₂ (F _I O ₂ = 1)	R-L SHUNT	FRC % OF EXPECTED VALUE
4 - 12 H	0.02 > P > 0.01	0.05 > P > 0.025	0.6 > P > 0.5
4 - 24 H	0.05 > P > 0.025	0.005 > P > 0.001	0.4 > P > 0.3

EVOLUTION OF FRC AND $\dot{Q}_S/\dot{Q}_T$ IN HMD



GRAPH 3

EVOLUTION OF FRC AND PaO_2
IN HMD
- FIRST 24 HOURS OF LIFE -



GRAPH 4

DISCUSSION AND CONCLUSIONS

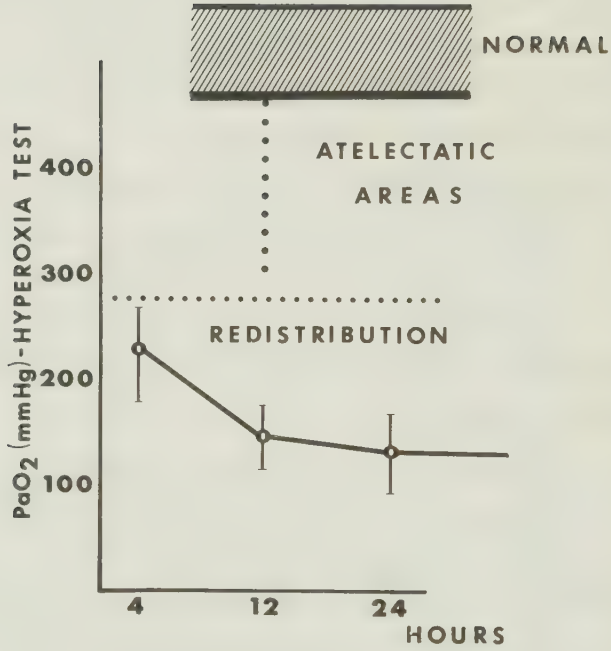
The low pulmonary aeration found in Hyaline Membrane Disease by other authors (3, 57) was confirmed in this study. However in an evolutionary study of the first 24 hours of life it was found that the atelectatic zones do not increase during this period of time. This is in disagreement with some authors (97), who postulated the increase in atelectasis as an explanation for the increase of the R-L shunt (fall of the PaO_2).

Even if the absolute values of the right to left shunt cannot be accurately calculated by our method (112, 113), it is a fact that the important change of the right to left shunt between the 4th and the 24th hour of life is not accompanied by a simultaneous change of the functional residual capacity. For this reason, it seems to us unnecessary to get into further calculations as proposed by Gersony et al, (112).

In 6 infants with perinatal asphyxia without HMD, a similar study was carried out and a parallel evolution between R-L shunt and FRC (pulmonary aeration) was found. With the increase in FRC there was a decrease in percentage of R-L shunt (107). The atelectasis would increase vascular resistance in the pulmonary bed, thus reducing perfusion of the collapsed areas (9, 78). This would be the real hypoperfusion syndrome of Chu and all (19).

In the 24 infants with HMD there was a constant raise of the R-L shunt (fall of the PaO_2) with no significant change in FRC.

From this it can be postulated - graph 5 - that the initial low PaO_2 values are due to the atelectatic areas in the lungs, but the subsequent fall is due to a redistribution of blood through the fetal paths foramen ovale and ductus arteriosus.



GRAPH 5

THE EFFECTS OF REDISTRIBUTION OF INTRA-PULMONARY
TO EXTRA-PULMONARY SHUNTING ON PaO_2

THE EARLY STAGES OF H M D

III. EVOLUTION OF THIRTEEN PARAMETERS
IN THE FIRST 48 HOURS OF LIFE AND
DISCRIMINANT ANALYSES

by

N. FRENCK, L. AUER and L.S. PROD'HOM*

Clinique Infantile Universitaire

Département d'Informatique Hospitalière

Switzerland

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INTRODUCTION

It is important to know the natural history of the Hyaline Membrane Disease (HMD) in order to make as early as possible a mortality prognosis and a morbidity prognosis to avoid preventable accidents.

Thirteen parameters were taken into account and they were followed for the first 48 hours of life. The analysis were carried out at 2, 4, 12, 24, 36, 48, and 96 hours of life.

The 13 parameters were the following :

- a) Gestational age (in weeks)
- b) Birth Weight (in grams)
- c) Hours of life
- d) Hemoglobin (in grams %)
- e) SaO_2
- f) PaO_2 (in mmHg)
- g) R-L shunt (in %)
- h) PaCO_2 (in mmHg)
- i) Base Excess
- j) pH
- k) Asphyxia or not (1 = asphyxia, 0 = no asphyxia)
- l) X-Ray stage (1 to 4)
- m) Dead or not (1 = dead, 0 = surviving)

The criteria for asphyxia were : APGAR score less than 4 at 1', or a score of 6 or less at 5 minutes : delay in the first breath of more than 25"; no spontaneous respiration after mask assistance and

or need for intubation at birth (57, 78).

pH was measured with a pH glass electrode (3) and the PCO_2 and BE were calculated on the Siggaard-Anderson curve nomogram (2, 3, 84, 89, 90).

The R-L shunt was calculated by Berggren's modification (23, 22) of the basic shunt equation, see companion paper.

Two discriminant analysis were performed in order to determine if the groups of babies already separated according to gestational age and perinatal asphyxia were statistically different.

A third discriminant analysis was done on babies that died in the course of the disease and those surviving. The purpose of this analysis was to see the importance of each parameter for predicting the probability of survival already at the 4th hour of life.

The data were examined in order to find out the importance of each parameter for the separation of each couple of groups.

Few discriminant analysis were previously performed in order to figure out the probability of survival of infants with HMD (95, 107). In one of them (95), babies have been examined between 0 and 12 hours of life and in the other one (107) the hour of life was not considered at all.

STATISTICAL METHODS

A discriminant function $z = \sum_{i=1}^n l_i x_i$ was calculated,

where n = number of parameters taken into account

l_i = linea compound

x_i = value of parameter i (a to m)

The linea compounds were calculated in order to make the ratio D^2 as large as possible.

$$D^2 = \frac{(\bar{z}_A - \bar{z}_B)^2}{\text{variance of } z \text{ within groups}}$$

D = generalised distance between the two groups.

Knowing z it was possible to calculate u , which is a standard variable with mean = 0 and SD = 1, for each group A and B in order to construct hypothetical curves of normal distribution.

$$u_A = \frac{(z - \bar{z}_A)}{SD_{z_A}} \quad \text{and} \quad u = \frac{(z - \bar{z}_B)}{SD_{z_B}}$$

$$\text{then for each group } \varphi(u) = \frac{2}{\sqrt{2\pi}} e^{-\frac{u^2}{2}}$$

where $\bar{z}$ and SD_z are the mean and the standard deviate of a group,

while z is the value of the discriminant function for a given

baby, and $\varphi(u)$ is the value of the normal distribution curve at u .

The probability for these babies to belong to one or the other group was calculated.

$$\begin{aligned}
 - \text{Probability to belong to group A} &= \frac{\varphi(u_A)}{\varphi(u_A) + \varphi(u_B)} \\
 - \text{Probability to belong to group B} &= \frac{\varphi(u_B)}{\varphi(u_A) + \varphi(u_B)}
 \end{aligned}$$

The probability of error when choosing an arbitrary Z is a rule of decision to separate both groups is determined :

- α error = probability to class a true element of the first group wrongly in the second group.
- α error = probability to class a true element of the second group wrongly in the first one.

$$\text{If } \bar{z}_A \leq \bar{z}_B, \quad \alpha = 1 - \Phi(u_A) ; \beta = \Phi(u_B)$$

$$\text{If } \bar{z}_A > \bar{z}_B, \quad \alpha = \Phi(u_A) ; \beta = 1 - \Phi(u_B)$$

$$\text{where } \Phi(u) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t=u} e^{-\frac{t^2}{2}} dt$$

(u) represents the area under a normal distribution curve from $-\infty$ to u.

The discriminant analyses were performed in a IBM 360 Model 65 - computer at the International Computing Center of the World Health Organization, in Geneva. We are grateful to Mr. WEBER, Chef du Département d'Informatique Hospitalière, Hôpital Cantonal de Lausanne, and Mr. CUBINAT from the WHO, Geneva.

An example is given in graph 1 where a theoretical distribution of the discriminant function $Z = \sum_{i=1}^n l_i x_i$ at 4 hours of life was drawn for the groups of surviving babies and babies dying in the course of the disease.

In the upper part of the graph $\psi(u)$ is represented and the gaussian distribution of both groups shown.

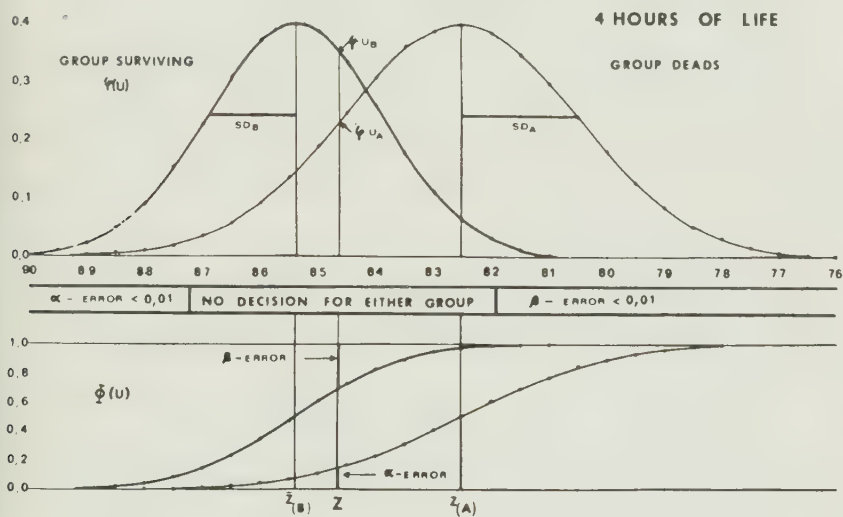
In the lower part of the graph $\Phi(u)$ was determined in order to find out α error and β error.

Between these two curves is shown the rule of decision with a midzone of no possible decision. Out of this midzone a decision can be made to include the baby in that group with a possibility of error of less than 0,01.

To find out Z in this particular case the following formula was used (a through l are the variables described in page 1).

$$\begin{aligned} Z = & a \times (-0.4435) + b \times 0.001069 + d \times 0.19246 + \\ & e \times 7.356 + f \times 0.0068018 + g \times (-0.001207) + \\ & h \times (0.15425) + i \times (-12.2549) + j \times 0.087362 + \\ & k \times 0.80922 + l \times 1.07862 \end{aligned}$$

THEORETICAL DISTRIBUTION OF THE DISCRIMINANT FUNCTION $Z = \sum_{i=1}^n x_i$



RESULTS

1. Babies with a gestational age of 33 weeks or less and more than 33 weeks.

Babies below 33 weeks gestation had a significantly lower birth weight ($p < 0.001$) than those over this gestational age, and there was an excellent correlation between gestational age and birthweight. The number of deaths was higher in babies with a gestational age of or below 33 weeks ($p < 0.001$). There was not a significant difference ($p < 0.2$) in the number of deaths among those with or without asphyxia at birth in this gestational age group. The same was found for babies with a gestational age of more than 33 weeks ($p < 0.1$).

The x-ray stage distribution was different ($p < 0.001$) in either group, the severity of the disease was more important in low gestational age babies.

The number of ventilated infants was higher in babies with 33 weeks gestation or less, but the number of deaths among ventilated was not significantly different in either group (see Table 1).

The groups of HMD with a gestational age of 33 weeks or less and HMD with more than 33 weeks were proven to be statistically different with a probability of error of less than 0.001. The most important discriminant parameters are shown in Table III.

At 4 hours of life a significant difference in PaO_2 , PaCO_2 , pH and x-ray stage was found. The evolution of the PaO_2 and its significance is described in the preceeding paper (see Table II).

- R-L shunt was larger in babies with a lower gestational age but the difference was not statistically significant.
- PaCO_2 was significantly ($p < 0.01$) higher in babies with 33 weeks gestation or less, at 4 hours of life. The difference persisted for the first 24 hours, by the 36th hour of life there was no difference at all.
- B.E. was bit different in either group.
- pH was lower in the 33 weeks gestation group during the first 24 hours of life but the difference was significant only at 4 hours of life. ($p < 0.05$).

The most important parameters and the standardised distance between them are described in Table III.

TABLE I

TOTAL		HMD $\leq 33w$	HMD $> 33w$	P
NUMBER	77	42 = 54,5 %	35 = 45,5 %	
GESTATIONAL AGE (WEEKS)	33,3	30,9 $\pm$ 0,24	36,2 $\pm$ 0,34	$P < 0,001$
BIRTH WEIGHT (GRAMS)	1939,9	1506,9 $\pm$ 51,6	2459,4 $\pm$ 81,4	$P < 0,001$
NUMBER OF DEADS	26 = 33,7 %	22 = 52,4 %	4 = 11,4 %	$P < 0,001$
NUMBER OF ASPHYXIATED	37 = 48,1 %	26 = 61,9 %	11 = 31,4 %	$0,001 < P < 0,05$
X - RAY STAGE	I	3 = 7,1 %	3 = 8,6 %	$P < 0,001$
	II	13 = 30,9 %	19 = 54,3 %	
	III	19 = 45,2 %	11 = 31,4 %	
	IV	7 = 16,6 %	2 = 5,7 %	
NUMBER OF VENT. INFANTS	35 = 45,4 %	26 = 61,9 %	9 = 25,7 %	$0,01 < P < 0,025$
NUMBER OF DEADS AMONG VENT.	23 = 65,9 %	20 = 76,9 %	3 = 33,3 %	$0,1 < P < 0,2$

TABLE II

GROUPS HMD 33 AND 33 WEEKS GESTATION

	4 hours					12 hours					24 hours				
	33		33			33		33			33		33		
Number	42		35			39		34							
	m	SD	m	SD	t	m	SD	m	SD	t	m	SD	m	SD	t
Gest. Age	30.9	1.57	36.2	2.02		31.1	1.56	36.3	2.01		31.3	1.31	36.24	2.05	
Weight in g.	1506.9	334.5	2459.4	481.3	10.21***	1534.1	361.3	2463.82	487.8	9.33***	1548.9	335.8	2438.4	73.25	8.46***
Hemoglobin	17.8	3.45	17.8	3.14	0.031	17.2	3.63	17.7	2.94	0.65	15.9	2.97	17.3	2.9	1.85
SeO ₂	0.89	0.16	0.94	0.1	1.53	0.84	0.2	0.90	0.14	1.50	0.87	0.16	0.92	0.14	1.17
PaO ₂	133.0	95.8	185.6	131.3	2.027*	105.3	70.95	150.21	101.4	2.22*	106.9	80.1	114.9	66.96	0.43
Paco ₂	62.5	17.7	52.1	13.9	2.84**	55.4	18.54	48.33	14.0	1.82	56.9	21.2	47.7	11.42	2.18*
B.E.	-7.8	5.54	-8.61	3.74	0.75	-4.33	5.47	-4.37	4.3	0.06	-3.37	5.00	-3.66	3.62	0.27
pH	7.17	0.12	7.22	0.08	2.13*	7.25	0.13	7.29	0.05	1.93	7.26	0.11	7.31	0.05	2.32*
R-L Shunt	41.11	18.9	34.7	16.3	1.58	48.3	20.97	42.08	18.1	1.36	47.4	18.4	43.7	14.4	0.91
X-Ray stage	2.71	0.83	2.34	0.73	2.06*	2.69	0.83	2.35	0.73	1.84	2.59	0.87	2.35	0.73	1.16
Asphyxia	0.62	0.49	0.31	0.47	2.76**	0.59	0.5	0.32	0.47	2.33*	0.52	0.51	0.32	0.47	1.56
Dead	0.52	0.51	0.11	0.32	4.14***	0.49	0.51	0.12	0.33	3.64***	0.34	0.48	0.09	0.29	2.60*

$t_{0.05}^* = 1.992$
 $t_{0.01}^{**} = 2.643$
 $t_{0.001}^{***} = 3.435$

$t_{0.05}^* = 1.994$
 $t_{0.01}^{**} = 2.647$
 $t_{0.001}^{***} = 3.433$

$t_{0.05}^* = 1.997$
 $t_{0.01}^{**} = 2.659$
 $t_{0.001}^{***} = 3.457$

TABLE III

DISCRIMINANT PARAMETERS FOR

GROUPS HMN 33 AND 33 WEEKS GESTATION

4 hours		12 hours		24 hours	
Most important parameters	Stand. distance between the most import. param.	Most important parameters	Stand. distance between the most import. param.	Most important parameters	Stand. distance between the most import. param.
Birth weight	2.336	Birth weight	- 2.188	Birth weight	-2.139
Dead	0.947	Dead	0.855	Dead	0.658
PaO ₂	0.649	Asphyxia	0.546	pH	0.586
Asphyxia	0.632	PaO ₂	0.519	PaO ₂	0.552
pH	0.488	pH	0.452	Hemoglobin	0.469
X-Ray stage	0.472	X-Ray stage	0.431	Asphyxia	0.395
PaO ₂	0.464	PaO ₂	0.427	SaO ₂	0.297
R-L Shunt	0.361	SaO ₂	0.353	X-Ray stage	0.292
SaO ₂	0.350	R-L Shunt	0.319	R-L Shunt	0.229
B.I.	0.171	Hemoglobin	0.153	PaO ₂	0.109
Hemoglobin	0.0070	B.E.	0.0147	B.E.	0.067

II. Babies presenting HMD + asphyxia at birth versus babies
with HMD without asphyxia

The first ones had a shorter gestational age and the number of deaths was significantly higher than in the non-asphyxiated group.

There was not a significant difference in mortality of asphyxiated babies following their gestational age ($p < 0.1$). Among the non-asphyxiated babies the mortality was higher ($p < 0.02$) in babies with a gestational age of 33 weeks or less.

The x-ray stage distribution was significantly different in either group; among the asphyxiated there was a higher number of stage III and IV, while in the non-asphyxiated there was a higher number of stage II and I.

The number of ventilated infants was three times higher in the asphyxiated group and this difference was highly significant; but the number of deaths among ventilated was not significantly different in each group (a summary is given in Table IV).

The classes means of HMD + asphyxia and HMD without asphyxia were proven to be statistically different with a probability of error of < 0.001 at 4, 12 and 24 hours of life, but there was a certain degree of overlapping of the two groups.

The most important discriminant parameters with the standardised distance between the means of each group are shown in Table V.

At 4 hours of life a significant difference in R-L shunt, chest x-ray stage, SaO_2 , PaO_2 , weight in grams and gestational age was found. The means, standard deviations and t-test of significance are given in Table VI.

Babies with HMD + asphyxia had a significantly larger R-L shunt than the non-asphyxiated, but by 12 hours of life this difference was no longer significant.

PaO_2 was much higher in non-asphyxiated babies ($p < 0.001$) at 4 hours of life, the difference decreased but was still significant ($p < 0.01$) by 12 hours and was no longer significant at 24 hours of life (see companion paper).

pH was lower in the asphyxiated babies ($p < 0.05$) at the fourth hour of life but by the 12th hour it was the same for both groups. No significant B.E. or PaCO_2 differences were found.

T A B L E IV

HMD
+
TOTAL
ASPHYXIA

HMD
WITHOUT
ASPHYXIA

P

NUMBER	77	37 = 48 %	40 = 51,9 %	
GESTATIONAL AGE (WEEKS)	33,3	32,3 ± 0,5	34,2 ± 0,5	P < 0,01
BIRTH WEIGHT (GRAMS)	1939,9	1733,5 ± 97,9	2130,7 ± 94,7	P < 0,01
NUMBER OF DEADS	26 = 33,7 %	19 = 51,3 %	7 = 17,5 %	0,005 > P > 0,001
X - RAY STAGE	I	1 = 2,7 %	5 = 12,5 %	0,005 > P > 0,001
	II	11 = 29,7 %	21 = 52,5 %	
	III	16 = 43,2 %	14 = 35,0 %	
	IV	9 = 24,3 %	0 = 0 %	
NUMBER OF VENTILATED INFANTS	35 = 45,4 %	26 = 70,2 %	9 = 22,5 %	P < 0,0005
NUMBER OF DEAD AMONG VENTILATED	23 = 65,7 %	18 = 69,2 %	5 = 55,5 %	N.S.

TABLE V

DISCRIMINANT PARAMETERS FOR

GROUPS HMD + ASPHYXIA - HMD WITHOUT ASPHYXIA

4 hours		12 hours		24 hours	
Most important parameters	Stand. distance between the most import. param.	Most important parameters	Stand. distance between the most import. param.	Most important parameters	Stand. distance between the most import. param.
R-L Shunt	1.3739	X-Ray stage	0.8853	X-Ray stage	0.6902
SaO ₂	-1.0708	Dead or not	0.6505	Birth weight	-0.4379
PaO ₂	-1.0327	PaO ₂	-0.6371	Dead or not	0.4291
X-Ray stage	0.9070	Birth weight	-0.6152	Gest. Age	-0.3647
Dead or not	0.7564	Gest. Age	-0.5418	B.E.	0.3432
Birth weight	-0.6650	SaO ₂	-0.4782	PaO ₂	-0.3142
Gest. Age	-0.6043	R-L Shunt	0.4251	Hemoglobin	-0.1661
pH	-0.4679	Hemoglobin	-0.3300	SaO ₂	-0.1288
PCO ₂	0.3862	B.E.	0.0853	R-L Shunt	-0.1250
Hemoglobin	-0.3309	pH	-0.0255	pH	0.0451
B.E.	0.0108	PCO ₂	0.0159	PCO ₂	0.0057

TABLE VI

GROUPS HMD + ASPHYXIA - HMD WITHOUT ASPHYXIA

4 hours					12 hours					24 hours									
HMD+ASPH.					HMD					HMD+ASPH.					HMD				
Number	37		40		34		39		26		37		t						
	m	SD	m	SD	m	SD	m	SD	t	m	SD	m	SD	t					
Post. Age	32.3	3.1	34.2	3.1	32.6	3.0	34.3	3.1	2.7**	33.3	3.0	34.4	3.0	1.42					
Weight in g.	1734	595.1	2131	599.1	1768.2	606.6	2140.5	603.8	2.6**	1875	628.3	2137	577.6	1.7					
Hemoglobin	17.2	4	18.2	3	16.9	3.8	17.9	2.8	1.4	16.4	3.1	16.9	2.9	0.6					
SAO ₂	0.853	0.166	0.978	0.02	0.827	0.207	0.910	0.137	2.03*	0.884	0.15	0.902	0.14	0.5					
FaO ₂	101.6	78.7	208.1	121.3	97.2	73.4	151.5	94.1	2.71**	97.8	60.2	120.7	79.9	1.22					
PaCO ₂	61.1	19.7	54.7	13.2	52.27	13.5	52.0	19.6	0.06	52.0	11.3	51.9	20.5	0.02					
B.W.	-8.1	5.7	-8.2	3.9	-4.1	5.9	-4.5	3.89	0.003	-2.7	4.7	-4.12	3.9	1.34					
pH	7.16	0.12	7.21	0.07	7.27	0.11	7.27	0.09	0.10	7.29	0.08	7.28	0.08	0.017					
R-L Shunt	48.8	19.1	28.4	9.4	49.8	21.6	41.5	17.3	1.81	46.7	16.6	44.6	16.3	0.48					
X-Ray stage	2.89	0.81	2.23	0.7	2.88	0.81	2.23	0.67	3.7***	2.8	0.87	2.24	0.68	2.69**					
	$t_{0.05^*} = 1.992$				$t_{0.05^*} = 1.994$				$t_{0.05^*} = 1.997$										
	$t_{0.01^{**}} = 2.643$				$t_{0.01^{**}} = 2.647$				$t_{0.01^{**}} = 2.659$										
	$t_{0.001^{***}} = 3.425$				$t_{0.001^{***}} = 3.433$				$t_{0.001^{***}} = 3.457$										

III. Babies that died in the course of the disease and
those surviving

The classes of babies with HMD that died and of HMD that survived were also proven to be statistically different with a probability of error of ≤ 0.001 at 4, 12 and 24 hours of life. The difference in gestational age and in birthweight in both groups was very significant ($p \leq 0.001$). The babies dying in the course of the disease had a shorter gestational age and a lower birthweight than the surviving ones.

The percentage of asphyxiated babies in the dying group was more than twice that of the surviving group ($0.001 \leq p \leq 0.005$). The number of ventilated infants among the dying group was higher than in the surviving group ($p \leq 0.0005$).

The distribution of x-ray stage was significantly different ($0.005 \leq p \leq 0.001$) in each group (see Table VII).

At 4 hours of life there was a mixed acidosis in both groups, but the respiratory component was more important in the dying group; the difference in PaCO_2 was highly significant ($p \leq 0.001$).

R-L shunt was more important in the babies with HMD that died than in the surviving ones, and the difference increased in the first 24 hours becoming very significant ($p \leq 0.001$) by the 12th hour of life.

The first PaO_2 value was lower in the dying group and the subsequent fall was more important in this group than in the surviving ones. By the 12th hour of life, the difference was very significant ($p = 0.001$).

The most important discriminant parameters with the standardised distance between them are described in Table VIII.

The means, standard deviations and t-test of significance are shown in Table IX.

T A B L E V I I

TOTAL		HMD DEAD	HMD SURVIVING	P
NUMBER	77	26 = 33,8 %	51 = 66,2 %	
GESTATIONAL AGE (WEEKS)	33,3	31,4 ± 0,5	34,3 ± 0,4	P < 0,001
BIRTH WEIGHT (GRAMS)	1939,9	1606,5 ± 109	2109,8 ± 81,9	P < 0,001
NUMBER OF ASPHYXIATED	37 = 48,1 %	19 = 73 %	18 = 35,3 %	0,005 > P > 0,001
X - RAY STAGE	I	6 = 7,7 %	5 = 9,8 %	0,005 > P > 0,001
	II	32 = 41,5 %	27 = 52,9 %	
	III	30 = 38,9 %	18 = 35,3 %	
	IV	9 = 11,6 %	1 = 1,96 %	
NUMBER OF VENTILATED INFANTS	35 = 45,4 %	23 = 88,3 %	12 = 23,5 %	P < 0,0005

TABLE VIII

DISCRIMINANT PARAMETERS FOR

GROUPS HMD DEAD - HMD SURVIVING

4 hours		12 hours		24 hours	
Most important parameters	Stand. distance between the most import. param.	Most important parameters	Stand. distance between the most import. param.	Most important parameters	Stand. distance between the most import. param.
X-Ray stage	1.0250	R-L Shunt	1.4059	R-L Shunt	1.7973
Gest. Age	-0.9604	SaO ₂	-1.3304	SaO ₂	-1.5361
PCO ₂	0.8707	PaO ₂	-1.1725	pH	-1.4760
Birth weight	-0.8643	X-Ray stage	1.0236	X-Ray stage	1.0495
pH	-0.7992	Gest. Age	-0.8766	PaO ₂	-0.9767
Asphyx. or not	0.7992	pH	-0.8506	Birth weight	-0.7290
R-L Shunt	0.6827	Birth weight	-0.8024	Gest. Age	-0.5998
SaO ₂	-0.5036	Asphyx. or not	0.6986	B.E.	-0.5949
PaO ₂	-0.4054	B.E.	-0.4220	PCO ₂	0.5565
Hemoglobin	-0.1704	PCO ₂	0.3466	Asphyx. or not	0.5220
B.E.	-0.0170	Hemoglobin	-0.2417		

DISCUSSION

The arbitrary separation of babies above and below 33 weeks gestation was done in view of the results obtained monitoring PaO_2 in this two age groups. The good correlation of gestation age and birth weight was the proof that the babies were appropriate for dates.

The group of babies below 33 weeks gestation was in a worst shape at or before the 4th hour of life : the x-ray stage was more severe and the number of asphyxiated babies was higher.

A mixed acidosis was present at 4 hour of life in both groups but the respiratory component was more important in the lower gestational age group. This, together with a lower PaO_2 could be the signs of a mechanical respiratory insufficiency (softer thoracic cage and smaller muscular mass), the difference persisted for the first 24 hours of life.

The number of deads was significantly higher in babies 33 weeks gestation.

The second discriminant analysis was done in order to separate babies presenting H^+D + asphyxia and those presenting H^+D without asphyxia and to see if they were two significantly different groups.

Asphyxiated babies were smaller than those without asphyxia, they had a worse x-ray stage and 70,2 % of them needed artificial ventilation.

The absence of difference in BE can be explained by a very early correction of acidosis with bicarbonate in babies presenting asphyxia at birth. It would seem that although asphyxia is not the cause of HHD, it is probably one of the most important aggravating factors since 73 % of babies that died in the course of the disease were asphyxiated at birth.

From the results of the discriminant analysis of the group of babies that died in the course of the disease and those surviving it can be postulated that low birthweight and asphyxia are among the most handicapping factors.

In babies with a fatal outcome there is a steeper fall in PaO_2 and a persistent acidosis. The lowest the initial PaO_2 value (larger R-L shunt), the worst the prognosis (101).

The presence of a significantly higher PCO_2 before or at the 4th hour of life can be due either to a CNS problem (haemorrhage, depression of respiratory centers), or to an impossibility of small babies to perform a good ventilation. This high PCO_2 value was also found by other authors (95, 107).

The x-ray stage and the perinatal asphyxia are of paramount importance in the evaluation of the survival probability of HHD infants.

S U M M A R Y

77 babies presenting HMD were studied and three pairs of groups were done, taking into account gestational age, asphyxia and dead.

Thirteen parameters were examined; their evolution was followed and their importance was evaluated for the separation of each pair of groups.

The group of babies with a gestational age lower than 33 weeks is significantly different for babies presenting more than 33 weeks gestation. Babies with asphyxia at birth proved to be different from babies without asphyxia on the basis of the thirteen parameters. The same was true for the group of babies dying in the course of the disease and of those surviving. X-ray stage, gestational age, PaCO_2 and perinatal asphyxia are the most important criteria for calculating the probability of survival.

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